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## Case Report

## Alendronate-Induced Osteonecrosis of the Jaw in an Elderly Female

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## SUMMARY

**Background:** In recent years, more and more evidence has demonstrated that a rare symptom, osteonecrosis of the jaw, may be associated with long-term use of bisphosphonates. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) adversely affects the quality of life, producing significant morbidity in afflicted patients. The most common signs and symptoms are swelling, exposed bone, local infection, pathologic fracture of the jaw, etc.

**Patients and methods:** We report the case of an elderly female patient with alendronate-induced ONJ. After the patient discontinued taking bisphosphonates and her physician prescribed antiseptic mouthwashes and antibiotic drugs, her uncomfortable symptoms were relieved.

**Results:** This side effect rarely occurs in Taiwan; it causes permanent harm to patients. Moreover, it affects the normal function of taking food. Therefore, this article includes a case report and a list of some related papers systematically providing clinicians with a reference for future prescription of bisphosphonates.

**Conclusion:** Furthermore, we provide suggestions for the Mackay Memorial Hospital and dentists, in anticipation of earlier measures being taken in order to avoid bisphosphonate-related osteonecrosis, and to reduce additional medical expenses resulting from this side effect.

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## 1. Introduction

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a recently reported disease. The first cases of BRONJ associated with the use of oral bisphosphonates were reported in 2003<sup>1</sup>. Most of the reported cases were patients who received intravenous bisphosphonates. Only a few cases have been reported involving patients with osteoporosis receiving low-dose oral bisphosphonate therapy<sup>2</sup>. However, an increasing frequency of BRONJ has been reported in patients who received oral bisphosphonates<sup>3</sup>. BRONJ can remain asymptomatic for weeks or months and is recognized only by the presence of exposed bone in the oral cavity, which is sometimes painless<sup>2</sup>. The most commonly reported initiating factor for BRONJ development is tooth extraction, although periodontal disease and denture trauma have been implicated. Given the greater number of patients receiving oral bisphosphonates for the treatment of osteoporosis, it is likely that most doctors may encounter some patients with bisphosphonate-related osteonecrosis<sup>4</sup>. It is important to recognize the incidence of BRONJ in the

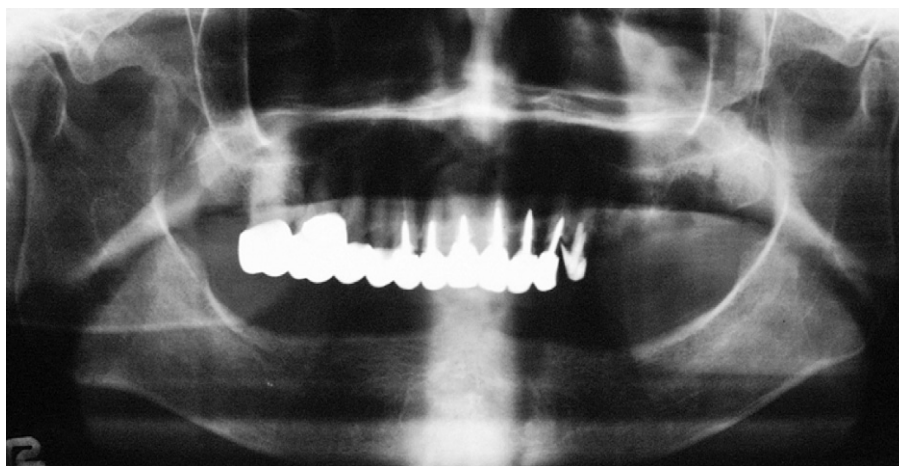
population and to assess the risk associated with long-term use, more than 3 years, of oral bisphosphonates<sup>4</sup>. In this article, we report the case of alendronate-induced BRONJ in an elderly female in Taiwan.

## 2. Case report

An 83-year-old female visited our department of oral and maxillofacial surgery in May 2008, with exposed bone over her upper jaw for several weeks. According to her statement and an old record, she had suffered from low back pain 5 years previously. Osteoporosis was diagnosed after examination in our neurosurgery department. A weekly drug containing alendronate 70 mg and colecalciferol 2800 IU (Fosamax Plus®) was prescribed and had been taken by the patient since then. She reported improvement in her symptoms and signs following the medication. However, she felt a painful swelling over the left maxillary molar area, and visited the oral and maxillofacial surgery department of another medical center. BRONJ was suspected, and therefore the patient discontinued Fosamax Plus®. Toothache persisted, however, and the patient visited local dental clinics in March 2008, where the left maxillary molars were extracted. Unfortunately, painful swellings and discharge with a bad odor were noted after the tooth extraction. Following visits to local clinics, she was referred to our oral

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**Fig. 1.** Dental panoramic roentgenogram reveals the irregular bone destruction over the left maxilla.

and maxillofacial surgery department for further evaluation. In our outpatient department (OPD), the patient was examined and a  $2 \times 1$  cm portion of necrotic maxillary alveolar bone was found to be exposed. There were no signs of infection, including alveolar osteitis, gingivitis/periodontitis and periapical pathologic findings close to the lesion. Dental panoramic radiography (Fig. 1) and facial bone computerized tomography (Fig. 2) revealed bony destruction over the left maxillary bone causing maxillary sinus reactive changes. According to the American Association of Oral and Maxillofacial Surgeons (AAOMS) *Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws (Position Paper)*, the patient was diagnosed with BRONJ. Conservative treatment included antiseptic chlorhexidine mouthwashes and antibiotic drugs to relieve her symptoms. A freed necrotic bone was removed 3 months after conservative treatment under local anesthesia without any complications. Pathological examination revealed sequestrum with bacteria colony. The wound healed uneventfully. No further bone was exposed and no discharge was noted during the following 1.5 years.

### 3. Discussion

BRONJ is a devastating side effect of long-term bisphosphonates. Oral bisphosphonates, which are used much more extensively than intravenous bisphosphonates, are prescribed for the treatment of bone resorption diseases, mainly osteopenia or osteoporosis<sup>5</sup>. Most cases of BRONJ occur in patients who are receiving the newer-generation nitrogen-containing bisphosphonates, including alendronate sodium. The mechanism of action of nitrogen-containing

bisphosphonates causing ONJ is starting to be recognized. These nitrogen-containing bisphosphonates are analogues of pyrophosphate; they have a high affinity to hydroxyapatite crystals and inhibit bone resorption. They also inhibit osteoclast activity and thus decrease bone remodeling<sup>2</sup>. Since the end of 2003, BRONJ has become an increasing problem and evidence of this trend is the increase in related case reports and a recently published case series<sup>6</sup>. BRONJ risks were categorized as drug-related, local, and demographic or systemic factors<sup>7</sup>. Drug-related risk factors include bisphosphonate potency and duration of therapy. Greater potency and longer duration appear to be associated with increased risk<sup>8,9</sup>. Furthermore, most cases of BRONJ are associated with long-term use of bisphosphonates. Thus, a dose-dependent and time-dependent relationship is thought to exist with respect to the disease process. Therefore, the longer a person is taking alendronate, the greater his or her risk of developing BRONJ<sup>3</sup>. Demographic factors, including age and race, and cancer diagnosis, with or without osteoporosis, were reported as risk factors for BRONJ<sup>7</sup>. Some studies reported increasing age as consistently being associated with BRONJ<sup>10</sup>. Sex was not statistically associated with BRONJ and race was reported to be a risk factor, with Caucasians having an increased risk for BRONJ compared with blacks<sup>11</sup>. Other related risk factors of BRONJ include intravenous bisphosphonates, cancer, anti-cancer therapy, duration of exposure, dental extractions, dental implants, poorly fitting dentures, glucocorticoids, smoking, and preexisting dental disease. This case met some of these conditions, including duration of exposure and dental extractions. To distinguish BRONJ from other delayed healing conditions, the following working definition of BRONJ was adopted by the AAOMS in 2009<sup>12</sup>. Patients may be considered to have BRONJ if



**Fig. 2.** Computerized tomographic scan reveals bony destruction over the left posterior maxilla (A) and left maxillary reactive sinus polyps formation (B).

all of the following characteristics are present: (1) current or previous treatment with a bisphosphonate; (2) exposed bone in the maxillofacial region that has persisted for more than eight weeks; and (3) no history of radiation therapy to the jaws. This case met all of the above-mentioned characteristics.

Here, we report a case of bone necrosis of the jaws in an Asian patient treated with tablets containing alendronate 70 mg and colecalciferol 2800 IU. According to the Naranjo causality assessment scale<sup>4</sup>, the following four reasons describe why the case was defined as probably BRONJ: (1) much evidence has already been published about BRONJ; (2) the patient developed the condition following approximately 5–7 years of treatment with alendronate; (3) the possibility of other medications causing BRONJ could be excluded because the patient took other medications simultaneously; and (4) her dentist made a diagnosis of BRONJ by panoramic radiography and computerized tomography.

The Naranjo causality assessment scale score was 6 in this case, which is defined as a probable adverse drug reaction. In other words, alendronate-induced BRONJ was identified in this case.

In Taiwan, one case was reported as BRONJ in 2007<sup>13</sup>. There were, however, several similar conditions. In this case, dental extraction was performed without any precaution – this may be the major cause of the BRONJ.

The conditions included the patient's age, a causal relationship of adverse drug reaction, and duration of bisphosphonate therapy. Based on the concept of patient medication safety, it is important for dentists to obtain and update all medical and medication histories regularly, and dentists should exercise caution in planning any dental procedures that may involve surgery, when patients are receiving bisphosphonate treatment. These procedures include periodontal surgical crown lengthening, periodontal osseous surgery, extractions, and placement of dental implants and hard tissue biopsies of the jawbones.

Recommendations for the prevention of BRONJ associated with oral bisphosphonates according to the AAOMS Taskforce are as follows<sup>12</sup>: (1) recent outcomes studies show improved outcome of BRONJ treatment with drug cessation<sup>14,15</sup>; (2) patient education and reassurance, control of pain, control of secondary infection, and prevention of extension of lesion and development of new areas of necrosis<sup>12</sup>; (3) it is recommended that patients be adequately informed of the small risk of compromised bone healing. The utilization of bone turnover marker levels in BRONJ, in conjunction with a drug holiday, has been reported as an additional tool to guide treatment decisions in patients exposed to oral bisphosphonates<sup>16</sup>; and (4) surgical debridement has been variably effective in eradicating the necrotic bone<sup>17,18</sup>. Patients with established BRONJ should avoid elective dentoalveolar surgical procedures, since these surgical sites may result in additional areas of exposed necrotic bone. The effectiveness of hyperbaric oxygen therapy as an adjunct to non-surgical and surgical treatment is under investigation at two institutions where a randomized, controlled trial is underway<sup>19</sup>.

Furthermore, we propose some suggestions for the Mackay Memorial Hospital and dentists in anticipation of earlier measures being taken in order to prevent BRONJ from occurring and to reduce additional medical expenses resulting from this side effect. We suggest that the Order Entry Systems of the Mackay Memorial Hospital should build up and provide warnings about BRONJ. The purpose of the Order Entry System is to remind our dentists that the AAOMS suggests that, when performing dentoalveolar surgery such as extractions and implants, patients who have taken oral bisphosphonates for more than 3 years should discontinue treatment for 3 months prior to performing the dental surgery and restart when the bone has healed. Meanwhile, dentists should educate patients about the importance of oral hygiene in order to avoid BRONJ from occurring.

In addition, the pharmacists should remind patients of one major precaution prior to dentoalveolar surgery. The major precaution is that they should actively quiz their dentist over taking bisphosphonates.

#### 4. Conclusion

In conclusion, an early diagnosis might prevent or reduce the morbidity resulting from advanced destructive lesions of the jaw bone. Meanwhile, long-term follow-up is necessary to care for patients on bisphosphonate therapy and patients with proven BRONJ.

Based on patient medication safety, all involved, including dentists orthopedic surgeons, pharmacists, the pharmaceutical company and the patients on bisphosphonate therapy, should be aware of BRONJ.

#### Conflict of interest

All contributing authors declare no conflict of interest.

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